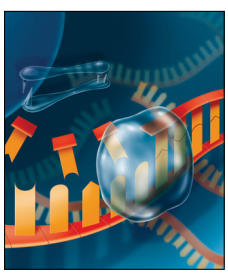
Host genetics shapes adult sepsis survival



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Sepsis is a major cause of death in adult intensive-care units (ICUs) worldwide,[1] despite the availability of a few highly effective therapeutic procedures. This syndrome develops as a result of a suspected or proven severe infection by different microorganisms (most commonly established intra-abdominally or in the lungs) and is characterised by a dysregulated non-specific acute inflammatory response, frequently leading to multiple organ failure.

The innate immunity responsiveness to an infection or to microbial products is shaped by the genetic differences between individuals, emphasising the crucial role of the host defence in the pathophysiology of this complex syndrome.[2,3] Such genetic differences could explain the diversity of clinical manifestations between patients with sepsis, and ultimately affect the mortality risk. One of the first findings supporting this possibility was obtained from epidemiological studies of adoption, in which adoptees showed an increased risk of death due to infections when one of their biological parents had died from infections.[4] Other studies in twins and siblings have supported this early finding, also revealing rather weak effects of host genetics on susceptibility to infections.[5]

Genetic studies have suggested that natural variants located in or nearby the genes encoding components of the pathogen-sensing machinery are associated with sepsis outcomes[2] and with sustained pro-inflammation after the setting of sepsis.[6] However, most, if not all, genetic factors that have been implicated so far in sepsis susceptibility or outcomes were found with limited screens of the genetic variation in candidates with the popular case-control study design. Despite the large number of such studies, re-analyses of the accumulated evidence did not show firmly associated genes.[7]

Genome-wide association studies (GWAS) are built on the same screening idea on a genomic scale, providing a reasonably unbiased method to find genetic risk factors for disease.[8] In *The Lancet Respiratory Medicine*, Anna Rautanen and colleagues[9] present the results from the first GWAS on survival from sepsis due to pneumonia, assessed in a multi-stage study including four cohorts and testing almost 6 million single nucleotide polymorphisms (SNPs). Using 28 day survival as a binary observation, the investigators identified SNPs from 11 loci with suggestive genome-wide significance in the discovery stage. Only one C/T SNP in chromosome 5, residing within the *FER* gene, showed consistent effects across the four cohort studies analysed. The C allele, with nearly 20% frequency in European populations, was associated with reduced mortality by sepsis caused by pneumonia with an unusually strong effect compared with those reported for genetic risks in other complex traits.[8] Importantly, the acute respiratory distress syndrome, a common sepsis-associated complication, was not a confounding factor for the observed effect.

The identified SNP in *FER* is intronic and has no evident functional consequences on the gene, as judging by the RegulomeDB and HaploReg. However, this situation is very common at the moment, since about 80% of identified risk variants in the published GWAS in complex diseases reside in intergenic or non-coding intronic regions.[8] Although the work by Rautanen and colleagues[9] did not provide a functional assessment of the top associated SNP, limiting a straightforward translation to the mechanism of disease, *FER* gene encodes a ubiquitously expressed non-transmembrane receptor tyrosine kinase. Since this kinase mediates in the actomyosin contractile machinery via growth factor receptors, regulating cell-cell adhesion and mediating neutrophil chemotaxis, its effects could be related to the host defense against pathogens or endothelial permeability. Since the identified SNP, or even the *FER* gene, might not be causally related to sepsis survival, further studies will be needed to address this point, as the genetic variation explored in the study only constitute a fraction of the real genetic diversity. Both, extensive sequencing of this genomic region to unravel unknown low-frequency variants with potential biological roles, and mechanistic understanding of the risk variants identified, will permit delineating the most likely causal variants. Additionally, in view of the reported ethnic disparities in sepsis incidence and mortality,[10] similar studies in samples of diverse geographical origin should be pursued to verify whether the *FER* SNP effect also pertains to sepsis survival in other populations.

Personalised medicine is based on the idea that if enough informative risk factors are known, more

For **RegulomeDB** see http://regulomedb.org

For **HaploReg** see http://www.broadinstitute.org/mammals/haploreg/haploreg_v3.php

effective risk stratification models can be devised. Many risk variants for sepsis survival await their discovery since the study by Rautanen and colleagues[9] was underpowered to detect all but the loci with the largest effects. Therefore, in view of our limited knowledge of the genes that contribute to shape the differences in sepsis survival between patients, and the poor prognostic utility of the identified *FER* genetic variant, this possibility is remote for now. To increase the power to detect additional risk variants underlying the diversity of sepsis manifestations, further genetic studies should focus on particular infections (source or causal pathogen), rather than on a broadly defined syndrome, and on specific traits related to severity and outcomes.

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Life behind the mask: the patient experience of NIV

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Over the past 30 years, non-invasive ventilation (NIV) has revolutionised the care of patients with acute and acute-on-chronic respiratory failure, and is now thought of as the standard of care. Improvements in survival and intubation rates are well established.[1] However, uncertainty remains as to whether NIV relieves subjective dyspnoea.[2] Whereas some patients adapt readily, others struggle. Development of a sound understanding of subjective experience for NIV might decrease intolerance and accelerate improvements in care.

Patient-centred care is increasingly recommended in policy, practice, and research.[3] Clinicians who understand the patient's experience are well placed to balance the potentially competing pressures of clinical indications and the comfort and preference of the patient. In interventions for which patient cooperation is crucial, such as NIV, this balance is essential. Despite this need for cooperation, little is known about what is happening behind the mask.

Two qualitative studies[4,5] from Scandinavian nurse-led research teams have analysed the behaviours adopted by patients adjusting to acute NIV. Both studies reported on patients with acute exacerbations of chronic obstructive pulmonary disease. Torheim and colleagues[4] analysed in-depth interviews with five patients who had recently received NIV, and noted that patients reported initial feelings of being trapped and completely dependent on others. Reports from patients suggested that skilled nursing assistance and mobilisation of internal resources, including willpower, helped them to gain control over their treatment and increase their tolerance of NIV.[4] Although this investigation is an important exploratory study, no attempt was made to reach thematic saturation (the point at which no additional themes are identified from the reviewing of successive data), which is a potential methodological limitation.

Sørenson and colleagues[5] studied 21 patients undergoing NIV and undertook 11 in-depth patient interviews to develop a behavioural model of the experience of treatment with NIV. This group also saw an initial phase in which patients felt restrained by the